514 Rec'd PCT/PTO 13 MAR 2000

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: P65123US0

US APPLICATION NO. (If known, see 37 CFR 1.5): 09/508083

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/05804	11 September 1998	12 September 1997

TITLE OF INVENTION: COMPOSITION FOR THE THERAPY OF DIABETES MELLITUS AND ADIPOSITY

APPLICANT(S) FOR DO/EO/US: Wolf-Georg FORSSMANN, Rudolf RICHTER, Knut ADERMANN and Markus MEYER

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

    International Search Report — EPO
    PCT/IB/301 Form
    PCT/IB/304 Form
    PCT/IB/308 Form
    First Page of Publication
    International Preliminary Examination Report — with Annexes in German

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US APPLICATION NO.(If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/508083	PCT/EP98/05804	P65123US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $760.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$970.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$840.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☒ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**37** - 20 =	**-17-**	x $18.00	$ 306.00	
Independent Claims	**3** - 3 =	-0-	x $78.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1276.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1276.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 1276.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 1276.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 1276.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ --- to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Wolf-Georg FORSSMANN et al

Serial No.: New

Filed: March 13, 2000

For: COMPOSITION FOR THE THERAPY OF DIABETES MELLITUS AND ADIPOSITY

PRELIMINARY AMENDMENT TO LESSEN FEES

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Claim 4, line 1, delete "any of claims 1 to 3",
insert --claim 1--;

Claim 5, line 1, delete "at least one of claims 1 to 4",
insert --claim 1--;

Claim 6, line 1, delete "at least one of claims 1 to 5",
insert --claim 1--;

Claim 7, line 1, delete "at least one of claims 1 to 6",
insert --claim 1--;

Claim 8, line 1, delete "at least one of claims 1 to 7",
insert --claim 1--;

Claim 9, line 1, delete "at least one of claims 1 to 8",
insert --claim 1--;

Claim 10, line 1, delete "at least one of claims 1 to 9",
insert --claim 1--;

Claim 11, line 1, delete "claims 1 to 10",
insert --claim 1--;

Claim 12, line 1, delete "claims 1 to 11",
insert --claim 1--;

Claim 13, line 1, delete "claims 1 to 12",
insert --claim 1--;

Claim 14, line 1, delete "claims 1 to 13",
insert --claim 1--;
Claim 15, line 1, delete "claims 1 to 14",
insert --claim 1--;
Claim 16, line 1, delete "claims 1 to 15",
insert --claim 1--;
Claim 17, line 1, delete "claims 1 to 16",
insert --claim 1--;
Claim 19, line 1, delete "or 18";
Claim 20, line 1, delete "any of claims 17 to 19",
insert --claim 17--;
Claim 21, line 1, delete "any of claims 17 to 20",
insert --claim 17--;
Claim 22, line 1, delete "any of claims 1 to 21",
insert --claim 1--;
Claim 23, line 1, delete "any of claims 2 to 22",
insert --claim 2--;
Claim 24, line 1, delete "any of claims 2 to 23",
insert --claim 2--;
Claim 25, line 1, delete "any of claims 2 to 24",
insert --claim 2--;
Claim 26, line 1, delete "any of claims 2 to 25",
insert --claim 2--;
Claim 27, line 1, delete "any of claims 2 to 26",
insert --claim 2--;

Claim 31, lines 2-3, change "any of claims 1 to 27 or a compound according to any of claims 28 to 30" to --claim 1--.

Add the following claims.

35. A medicament containing an effective amount of the compound of claim 31.

36. The medicament according to claim 35 characterized in that said medicament is in a release form by which release is achieved permanently or in a pulsatile way.

37. The medicament according to claim 36, characterized in that said medicament is suitable for subcutaneous, intravenous, peroral, intramuscular or transpulmonary administration.

REMARKS

The foregoing Preliminary Amendment is requested in order to delete the multiple dependent claims and avoid paying the multiple dependent claims fee.

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By _____
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Date: March 13, 2000
Atty. Docket: P65123US0
WEP:jrc

SMB

Composition for the Therapy of Diabetes Mellitus and Adiposity

The present invention relates to the composition of claims 1 to 29 and a medicament containing the compositions according to the invention.

The hormonal regulation of blood sugar homeostasis is effected primarily by the pancreatic hormones insulin, glucagon and somatostatin. They are produced in the islets of Langerhans in the pancreas. This endocrine regulation of the blood sugar level is in turn under the complex control by metabolites (glucose, amino acids, catecholamines, etc.) circulating with the blood. Although insulin secretion from the endocrine pancreas is predominantly stimulated by the blood glucose level, there are also paracrine factors in the form of hormones, such as glucagon and somatostatin, which affect insulin secretion. The modulation of insulin secretion in the islet cells of the pancreas is mediated by the second messenger cyclic adenosine monophosphate (cAMP).

The cAMP metabolism of the islet cells of the pancreas is regulated on different levels. On the one hand, the production of cAMP can be stimulated in the pancreatic beta cells, and on the other hand, the degradation of cAMP in the pancreatic beta cells can be stimulated or inhibited by various phosphodiesterases.

Phosphodiesterases are enzymes which degrade cyclic nucleotides (cAMP, cGMP). Today, a distinction is made between seven different groups of

phosphodiesterases which possess different substrate specificities and/or different mechanisms of activation/inhibition. For the different groups of phosphodiesterases, specific inhibitors have been described (for example: PDE I inhibitor: vinpocetin; PDE II inhibitor: trequinsin; PDE III inhibitor: milrinone; PDE IV inhibitor: rolipram; PDE V inhibitor: zaprinast).

Guanylin and uroguanylin are peptide hormones formed in the intestine which circulate in the blood. They belong to the guanylate cyclase activating peptides and stimulate the formation of cyclic guanosine monophosphate in various tissues.

Surprisingly, it has been found that a composition containing at least two of the following active substances A, B, C, wherein:

A = at least one hormone stimulating the production of cAMP;

B = at least one substance inhibiting the degradation of a cyclic nucleotide;

C = at least one hormone stimulating the production of cGMP;

is superior in therapy to the administration of the individual active substances.

The active substance A, for example, is a GLP-1/GLP-1-like peptide, preferably GLP-1(7-34)-amide and/or GLP-1(7-36)-amide. Surprisingly, the native plasma form GLP-1(7-34)-COOH and GLP-1(7-34)-amide have a half life which is twice to three times longer than that of GLP-1(7-36)-amide.

Further, infusion of GLP-1(7-34)-COOH and GLP-1(7-34)-amide in equimolar amounts results in a significantly higher insulin release and a signifi-

cantly higher reduction of the glucose level than the infusion of GLP-1(7-36)-amide does.

The active substance B, for example, is a phosphodiesterase inhibitor, preferably a group III and/or IV phosphodiesterase inhibitor.

Active substance C, for example, is a guanylate cyclase C activating peptide from the guanylin and/or uroguanylin genes, preferably guanylin-101-115 and/or uroguanylin-89-112.

The composition according to the invention can be employed in combination with one or more peptide hormones which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory peptide (GIP)/vaso-active intestinal peptide (VIP)/pituitary adenylate cyclase activating peptide (PACAP)/glucagon-like peptide II (GLP-II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related peptide (CGRP) gene family.

Preferably, the composition according to the invention is used with GLP-1 as GLP-1(7-34), GLP-1(7-35), GLP-1(7-36) or GLP-1(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-1 peptides with the following modifications:

(a) substitution of the amino acid lysine in position 26 and/or 34 by a neutral amino acid, arginine or a D-form of lysine or arginine; and/or substitution of arginine in position 36 by a neutral amino acid, arginine or a D-form of arginine or lysine;

(b) substitution of tryptophan in position 31 by an oxidation-resistant amino acid;

(c) at least one substitution in the following positions by the respectively stated amino acid:

Y for V in position 16;
K for S in position 18;
D for E in position 21;
S for G in position 22;
R for Q in position 23;
R for A in position 24; and
Q for K in position 26;

(d) at least one substitution in the following positions by the respectively stated amino acid:

a small neutral amino acid for A in position 8;
an acidic or neutral amino acid for E in position 9;
a neutral amino acid for G in position 10; and
an acidic amino acid for D in position 15; and/or

(e) substitution of the amino acid histidine in position 7 by a neutral amino acid or the D-form or N-acetylated or N-alkylated form of histidine wherein the amino acids for the stated substitutions are in either the D- or L-form, and the amino acid substituted in position 7 is substituted in either its N-acetylated or its N-alkylated form.

In another preferred embodiment, the composition according to the invention contains modifications from the exchange of amino acids in the D- or L-form. In particular, those modifications are possible in which the amino acid lysine in positions 26 and/or 34 is substituted by K†, G, S, A, L, I, Q, M, R and R†, and the amino acid arginine in position 36 is substituted by K, K†, G, S, A, L, I, Q, M and R†, and/or the amino acid tryptophan in position 31

is substituted by F, V, L, I, A and Y (the symbol † means the D-form of the corresponding amino acid).

Optionally, the modifications stated above may be combined with at least one of the substitutions S for G in position 22, R for Q and A in positions 23 and 24, and Q for K in position 26, or these substitutions may be additionally combined with a substitution of D for E in position 21.

Another modification is the substitution wherein alanine in position 8 is substituted by a small neutral amino acid from the group consisting of S, S†, G, C, C†, Sar, A†, beta-ala and Aib, wherein the acidic or neutral amino acid substituted for glutamic acid in position 9 is selected from the group consisting of E†, D, D†, Cay, T, T†, N, N†, Q, Q†, Cit, MSO and acetyl-K, and wherein the neutral amino acid substituted for glycine in position 10 is selected from the group consisting of S, S†, Y, Y†, T, T†, N, N†, Q, Q†, Cit, MSO, acetyl-K, F and F†.

A modification wherein the amino acid substituted for histidine in position 7 is selected from the group consisting of H†, Y, Y†, F, F†, R, R†, Orn, Orn†, M, M†, N-formyl-H, N-formyl-H†, N-acetyl-H, N-acetyl-H†, N-isopropyl-H, N-isopropyl-H†, N-acetyl-K, N-acetyl-K†, P and P† may also be used.

In particular, the following modified peptides may be used in the compositions according to the invention:
(H†)7-GLP-1(7-37), (Y)7-GLP-1(7-37), (N-acetyl-H)7-GLP-1(7-37), (N-isopropyl-H)7-GLP-1(7-37), (A†)8-GLP-1(7-37), (E†)9-GLP-1(7-37), (D)9-GLP-1(7-37), (D†)9-GLP-1(7-37), (F†)10-GLP-1(7-37), (S)22(R)23(R)24(Q)26-GLP-1(7-37), and/or (S)8(Q)9(Y)16(K)18(D)21-GLP-1(7-37).

Further, as the active substance A in the composition according to the invention, there may be used a peptide which has an increased resistance to degradation in the plasma as compared to GLP-1(7-34), GLP-1(7-35),

GLP-1(7-36) or GLP-1(7-37) or the C-terminal amide, and/or has at least one of the following modifications:
(α) substitution of histidine in position 7 by the D-form of a neutral or acidic amino acid or the D-form of histidine;
(β) substitution of alanine in position 8 by the D-form of an amino acid; and
(χ) substitution of histidine in position 7 by an N-acylated (1-6C) or N-alkylated (1-6C) form of an alternative amino acid or histidine.

Histidine in position 7 may be substituted by an amino acid from the group consisting of P†, D†, E†, N†, Q†, L†, V†, I† and H†, the D-amino acid in position 8 may be substituted by an amino acid from the group consisting of P†, V†, L†, I† and A†, and/or the D-amino acid in position 8 may be substituted by an alkylated or acetylated amino acid from the group consisting of P, D, E, N, Q, V, L, I, K, and H.

In another preferred embodiment, the composition according to the invention contains at least one modified peptide of the following type: (H†)7-GLP-1(7-37), (N-acetyl-H)7-GLP-1(7-37), (N-isopropyl-H)7-GLP-1(7-37), (N-acetyl-K)7-GLP-1(7-37) and/or (A†)8-GLP-1(7-37).

One skilled in the art will understand that the peptide active substances may be present in a phosphorylated, acetylated and/or glycosylated form.

In particular, those derivatives derived from GLP-1-(7-34)COOH and the corresponding acid amide are employed which have the following general formula:

$$R\text{-}NH\text{-}HAEGTFTSDVSSYLEGQAAKEFIAWLVK\text{-}CONH_2,$$

wherein R = H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are

the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.

As the active substance B in the composition according to the invention, there are employed, in particular, non-specific phosphodiesterase inhibitors, such as papaverine, theophylline, enprofyllines and/or IBMX, or specific phosphodiesterase inhibitors.

Particularly preferred are phosphodiesterase inhibitors which inhibit group III phosphodiesterases (cGMP-inhibited phosphodiesterases), such as indolidane (LY195115), cilostamide (OPC 3689), lixazinone (RS 82856), Y-590, imazodane (CI914), SKF 94120, quazinone, ICI 153,110, cilostazole, bemorandane (RWJ 22867), siguazodane (SK&F 94-836), adibendane (BM 14,478), milrinone (WIN 47203), enoximone (MDL 17043), pimobendane (UD-CG 115), MCI-154, saterinone (BDF 8634), sulmazole (ARL 115), UD-CG 212, motapizone, piroximone, ICI 118233, and/or phosphodiesterase inhibitors which inhibit group IV phosphodiesterases (cAMP-specific phosphodiesterases), such as rolipram ZK 62711; pyrrolidone), imidazolidinone (RO 20-1724), etazolate (SQ 65442), denbufylline (BRL 30892), ICI63197 and/or RP73401.

The phosphodiesterase inhibitors which can inhibit both group III and group IV phosphodiesterases, such as tolafentrine, zardaverine, EMD54622 and/or Org30029, can also be used in the composition according to the invention.

The medicament according to the invention contains an effective amount of the composition according to the invention and can be used for the therapy of insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, MODY (maturity-onset diabetes in young people), secondary hyperglycemias in connection with pancreatic diseases (chronic pancreatitis, pancreasectomy, hemochromatosis) or endocrine diseases (acromegaly, Cushing's syndrome, pheochromocytoma or hyperthyreosis), drug-induced

hyperglycemias (benzothiadiazine saluretics, diazoxide or glucocorticoids), pathologic glucose tolerance, hyperglycemias, dyslipoproteinemias, adiposity, hyperlipoproteinemias and/or hypotensions.

Surprisingly, the compositions according to the invention exhibit a significantly better therapeutical effect in diabetes mellitus, for example, than the monotherapies with the individual components.

Studies have shown that the compositions according to the invention lead to a significantly higher insulin release in animal experiments as compared to the individual components GLP-1, phosphodiesterase inhibitors, guanylin or uroguanylin. The blood sugar level is decreased by the composition according to the invention to a significantly higher extent than by the respective individual components. Further, it has been found that the therapeutic dosage of the compositions according to the invention, especially of GLP-1, could be significantly reduced. For the other components of the composition according to the invention, there is also a positive synergistic effect.

In animal experiments, it could be shown, surprisingly, that the duration of action of GLP-1 on the blood sugar level can be prolonged by a factor of 4 to 5 by combining it with phosphodiesterase or the guanylate cyclase activating peptides. These results are based on the determination of the blood sugar level upon one intravenous injection of the different combinations. Subsequently, the blood sugar level was determined over a period of 6 hours.

While GLP-1 must be continuously administered in a monotherapy, discontinuous delivery in a suitable dosage form can be achieved through the inventive combination with phosphodiesterases or guanylate cyclase activating peptides.

Surprisingly, it has been found in the studies that the therapeutically effective GLP-1 dosage is lower by a power of ten in the combination therapies as compared to the monotherapy with GLP-1. The side effects of GLP-1 monotherapy, especially delayed stomach discharge, could be eliminated both by phosphodiesterase inhibitors and by guanylin or uroguanylin.

Surprisingly, after a single application of the combination therapy, not only is the postprandial rise of the blood sugar level reduced, but also a subsequent decrease of the glucose level to an almost normal blood sugar level is achieved.

This shows that a continuous delivery of GLP-1 can be dispensed with in the combination according to the invention.

The compositions according to the invention with the individual components GLP-1, phosphodiesterase inhibitors, guanylin or uroguanylin were examined in vitro in a bioactivity assay. In this cellular assay, the formation of cAMP is examined. The compositions according to the invention gave a significantly higher level of cAMP formation in the assay as compared to the individual components.

Surprisingly, it has been found in studies on the functional mechanism of the action of guanylin and uroguanylin on insulin secretion that cGMP analogues result in an increase of the cAMP concentration in the islet cells.

Surprisingly, administration of the composition according to the invention will prolong the duration of action of the individual components.

The compositions according to the invention reduce the need for insulin in diabetes mellitus to a higher extent than is achieved by a corresponding

administration of individual components of the compositions according to the invention.

The compositions according to the invention are suitable for the therapy of insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, MODY (maturity-onset diabetes in young people), secondary hyperglycemias in connection with pancreatic diseases (chronic pancreatitis, pancreasectomy, hemochromatosis) or endocrine diseases (acromegaly, Cushing's syndrome, pheochromocytoma or hyperthyreosis), drug-induced hyperglycemias (benzothiadiazine saluretics, diazoxide or glucocorticoids), pathologic glucose tolerance, hyperglycemias, dyslipoproteinemias, adiposity, hyperlipoproteinemias and/or hypotensions.

The compositions according to the invention can be employed together with peptide hormones which are structurally related to glucagon, and/or with the peptide hormones adrenomedullin, amylin and/or calcitonin gene related peptide (CGRP). The hormones belonging to the glucagon multigene family are secretin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP), glucagon-like peptide II (GLP-II) and glicentin. These peptides regulate glucose metabolism, gastro-intestinal mobility and secretory processing in different ways. All gene products of secretin, GIP, VIP, PACAP, GLP-II, glicentin, adrenomedullin, amylin and CGRP as well as modified substances of secretin, GIP, VIP, PACAP, GLP-II, glicentin, adrenomedullin, amylin and CGRP can be used for such therapy.

For the therapy of diabetes mellitus or adiposity by the compositions according to the invention, GLP-1(7-34), GLP-1(7-35), GLP-1(7-36) or GLP-1(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-1 peptides with higher biological activity can be used.

For the therapy of diabetes mellitus or adiposity using the compositions according to the invention, as the active substance B, there may be used non-specific phosphodiesterase inhibitors, such as papaverine, theophylline, enprofyllines and/or IBMX; and/or specific phosphodiesterase inhibitors and especially those phosphodiesterase inhibitors which inhibit group III phosphodiesterases (cGMP-inhibited phosphodiesterases), including indolidane (LY195115), cilostamide (OPC 3689), lixazinone (RS 82856), Y-590, imazodane (CI914), SKF 94120, quazinone, ICI 153,110, cilostazole, bemorandane (RWJ 22867), siguazodane (SK&F 94-836), adibendane (BM 14,478), milrinone (WIN 47203), enoximone (MDL 17043), pimobendane (UD-CG 115), MCI-154, saterinone (BDF 8634), sulmazole (ARL 115), UD-CG 212, motapizone, piroximone, ICI 118233.

Further, there may be used phosphodiesterase inhibitors which inhibit group IV phosphodiesterases (cAMP-specific phosphodiesterases), such as rolipram ZK 62711; pyrrolidone), imidazolidinone (RO 20-1724), etazolate (SQ 65442), denbufylline (BRL 30892), ICI63197, RP73401.

Phosphodiesterase inhibitors which inhibit both group III and group IV phosphodiesterases, such as tolafentrine, zardaverine, EMD54622, Org30029, can also be used.

In vitro examinations on RIN cells surprisingly showed that specific PDE II and PDE IV inhibitors, in particular, inhibit the degradation of cAMP.

The combination of specific PDE II inhibitors and GLP-1-(7-34) induces a 5 to 10 times higher intracellular cAMP concentration as compared to administration of the individual substances. Further, it could be shown that the combination of specific PDE IV inhibitors and GLP-1-(7-34) induces a 10 to 15 times higher intracellular cAMP concentration as compared to administration of the individual substances.

As the active substance C, guanylate C activating peptides from the guanylin and/or uroguanylin genes, preferably guanylin-101-115 and/or uroguanylin-89-112, can be used.

For the therapy of diabetes mellitus or adiposity using the compositions according to the invention, the gene products of guanylin and uroguanylin or modified, more biologically active molecules of guanylin and/or uroguanylin may be employed.

The combination of specific PDE II inhibitors and guanylin induces a 2 to 3 times higher intracellular cAMP concentration as compared to the individual substance PDE II inhibitor and a 5 to 7 times higher intracellular cAMP concentration as compared to the individual substance guanylin. Further, it could be shown that the combination of specific PDE IV inhibitors and guanylin induces a 2 to 3 times higher intracellular cAMP concentration as compared to the individual substance PDE IV inhibitor and a 10 to 15 times higher intracellular cAMP concentration as compared to the individual substance guanylin.

Similarly, the pharmacologically acceptable salts are obtained by neutralization of the bases with inorganic or organic acids. As inorganic acids, there may be used, for example, hydrochloric, sulfuric, phosphoric or hydrobromic acid, and as organic acids, there may be used, for example, carboxylic, sulfo or sulfonic acids, such as acetic, tartaric, lactic, succinic, alginic, benzoic, 2-phenoxybenzoic, 2-acetoxybenzoic, cinnamic, mandelic, citric, malic, salicylic, 3-aminosalicylic, ascorbic, embonic, nicotinic, isonicotinic or oxalic acid, amino acids, methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, ethane-1,2-disulfonic, benzenesulfonic, 4-methylbenzenesulfonic or naphthalene-2-sulfonic acid.

For the preparation of the medicaments for the treatment of the mentioned diseases, a therapeutically effective combination of the individual sub-

stances or their salts is used, in addition to the usual auxiliary agents, carriers and additives. The dosage of the combination preparation depends on the species, body weight, age, individual condition of the patient and the way of administration.

Peptide containing medicaments are prepared by the method known to those skilled in the art for suitable ways of administration. Thus, in particular, oral, intravenous, intramuscular, intracutaneous, intrathecal and transpulmonary administrations may be used. The dosage to be administered for GLP-1 and its analogues is preferably from 0.1 µg per kg of body weight to 10 mg per kg of body weight. The dosage to be administered for guanylin and its analogues is preferably from 0.1 µg per kg of body weight to 10 mg per kg of body weight. The dosage to be administered for uroguanylin and its analogues is preferably from 0.1 µg per kg of body weight to 10 mg per kg of body weight. The peptides packaged in micelles and biopolymers may also be used as dosage forms.

In addition, known release forms by which release from galenic dosage forms of the ingredients is achieved permanently or in a pulsatile way may also be used for administration. Preferably, they include biopolymers as carriers, liposomes as carriers or infusion pumps so that administration can be effected, inter alia, subcutaneously, intravenously, perorally, intramuscularly or transpulmonarily.

Solid dosage forms may contain inert auxiliary agents and carriers, such as calcium carbonate, calcium phosphate, sodium phosphate, lactulose, starch, mannitol, alginate, gelatin, guar gum, magnesium or aluminum stearate, methylcellulose, talcum, highly dispersed silicic acid, silicone oil, higher molecular weight fatty acids (such as stearic acid), agar-agar or vegetable or animal fats and oils, solid high molecular weight polymers (such as

polyethylene glycol); formulations suitable for oral administration may also contain additional flavoring agents and/or sweeteners, if desired.

Liquid dosage forms may be sterilized and/or optionally contain auxiliary agents, such as preservatives, stabilizers, wetting agents, penetration agents, emulsifiers, spreading agents, solubilizers, salts for controlling the osmotic pressure or for buffering, and/or viscosity modifiers.

Such additives include, for example, tartrate and citrate buffers, ethanol, complexing (chelating) agents (such as ethylenediaminetetraacetic acid and its non-toxic salts). For controlling viscosity, there may be used high molecular weight polymers, such as liquid polyethylene oxide, carboxy-methylcelluloses, polyvinylpyrrolidones, dextranes or gelatin. Solid carriers include, for example, starch, lactulose, mannitol, methylcellulose, talcum, highly dispersed silicic acid, higher molecular weight fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular weight polymers (such as polyethylene glycol).

Oily suspensions for parenteral applications may contain vegetable, synthetic or semisynthetic oils, such as liquid fatty acid esters having from 8 to 22 carbon atoms in the fatty acid chains, for example, palmitic, lauric, tridecanoic, margaric, stearic, arachic, myristic, behenic, pentadecanoic, linolic, elaidic, brassidic, erucic or oleic acid, esterified with mono- to trihydric alcohols having from 1 to 6 carbon atoms, such as methanol, ethanol, propanol, butanol, pentanol or their isomers, glycol or glycerol. Such fatty acid esters include, for example, commercial miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG-6 caprate, caprylic/capric acid esters of saturated fatty alcohols, polyoxyethylene glycol trioleates, ethyl oleate, wax-like fatty acid esters, such as artificial duck uropygial gland fat, coconut oil fatty acid isopropyl ester, oleic acid oleyl

ester, oleic acid decyl ester, lactic acid ethyl ester, dibutyl phthalate, adipic acid diisopropyl ester, polyol fatty acid ester, etc. Also suitable are silicone oils of different viscosities or fatty alcohols, such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol or oleyl alcohol, fatty acids, such as oleic acid. Further, vegetable oils, such as castor oil, almond oil, olive oil, sesame oil, cottonseed oil, peanut oil or soybean oil, may also be used.

As a solvent, gelling agent and solubilizer, there may be used water or water-miscible solvents. Suitable solvents include, for example, alcohols, such as ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethylene glycol, waxes, methylcellosolve, cellosolve, esters, morpholine, dioxan, dimethyl sulfoxide, dimethylformamide, tetrahydrofuran, cyclohexane etc.

As film-forming agents, there may be used cellulose ethers which are soluble or swellable both in water and in organic solvents and, after drying, form a kind of film, such as hydroxypropylcellulose, methylcellulose, ethylcellulose or soluble starches. Thus, mixed forms between gelling agents and film-firming agents are also possible. Mainly, ionic macromolecules are employed, such as sodium carboxymethylcellulose, poly(acrylic acid), poly(methacrylic acid) and their salts, sodium amylopectin semiglycolate, alginic acid or propylene glycol alginate as the sodium salt, gum arabic, xanthane gum, guar gum or carrageen.

Further formulation aids that may be used include glycerol, paraffins of different viscosities, triethanolamine, collagen, allantoin, novantisolic acid, perfume oils.

The use of surfactants, emulsifiers or wetting agents may also be necessary for formulation, for example, sodium laurylsulfate, fatty alcohol ether sulfates, disodium N-lauryl-β-iminodipropionate, polyoxyethylated castor oil, or sorbitan monooleate, sorbitan monostearate, cetyl alcohol, lecithin,

glycerol monostearate, polyethylene stearate, alkylphenol polyglycol ether, cetyltrimethylammonium chloride or mono-/dialkyl polyglycol ether ortho-phosphoric acid monoethanolamine salts.

Stabilizers, such as montmorillonite or colloidal silica, for the stabilization of emulsions or for preventing the degradation of the active substances, such as antioxidants, for example, tocopherols or butylhydroxyanisol, or preservatives, such as p-hydroxybenzoic acid ester, may also be necessary for preparing the desired formulations.

The manufacturing, filling and sealing of the preparations are performed under the usual antimicrobial and aseptic conditions. If possible, the preparations are packaged in separate unit doses for facilitating the handling; in this case too, as for the parenteral forms, if necessary for reasons of stability, the active substances or their combinations are separately packaged as a lyophilizate, optionally with solid carriers and the necessary solvents, etc.

Sequence Listing

(1) General information:

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(F) Postal code: 30625

(ii) Title of invention: Composition for the therapy of diabetes mellitus and adiposity

(iii) Number of sequences: 1

(iv) Computer readable form:

(A) Medium type: Floppy disk

(B) Computer: IBM PC compatible

(C) Operating system: PC-DOS/MS-DOS

(D) Software: PatentIn Release #1.0, Version #1.30 (EPO)

(2) Information for SEQ ID NO: 1:

(i) Sequence characteristics:

(A) Length: 28 amino acids

(B) Type: amino acid

(C) Strandedness: unknown

(D) Topology: unknown

(ii) Type of molecule: peptide

(xi) Sequence description: SEQ ID NO: 1:

```
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1               5                  10                  15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys
            20                  25
```

CLAIMS:

1. A composition containing the following active substances A and C, wherein:

   A = at least one GLP-1/GLP-1-like peptide, preferably GLP-1(7-34)-amide and/or GLP-1(7-36)-amide;

   C = at least one guanylate cyclase C activating peptide from the guanylin and/or uroguanylin genes, preferably guanylin-101-115 and/or uroguanylin-89-112.

2. The composition according to claim 1, characterized by additionally containing an active substance B which is a substance inhibiting the degradation of a cyclic nucleotide.

3. The composition according to claim 2, wherein the active substance B is a phosphodiesterase inhibitor, preferably a group III and/or IV phosphodiesterase inhibitor.

4. The composition according to any of claims 1 to 3 in combination with one or more peptide hormones which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory peptide (GIP)/vasoactive intestinal peptide (VIP)/pituitary adenylate cyclase activating peptide (PACAP)/glucagon-like peptide II (GLP-II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related peptide (CGRP) gene family.

5. The composition according to at least one of claims 1 to 4, wherein the active substance A is GLP-1 and is used as GLP-1(7-34), GLP-1(7-

35), GLP-1(7-36) or GLP-1(7-37) in its C-terminally carboxylated or amidated form.

6. The composition according to at least one of claims 1 to 5, wherein, in the active substance GLP-1, the amino acid lysine in position 26 and/or 34 is substituted by a neutral amino acid, arginine or a D-form of lysine or arginine; and/or arginine in position 36 is substituted by a neutral amino acid, arginine or a D-form of arginine or lysine.

7. The composition according to at least one of claims 1 to 6, wherein, in the active substance GLP-1, tryptophan in position 31 is substituted by an oxidation-resistant amino acid.

8. The composition according to at least one of claims 1 to 7, wherein, in the active substance GLP-1, at least one amino acid given for the respective position is respectively substituted by following amino acids:

Y for V in position 16;
K for S in position 18;
D for E in position 21;
S for G in position 22;
R for Q in position 23;
R for A in position 24; and
Q for K in position 26.

9. The composition according to at least one of claims 1 to 8, wherein, in GLP-1, at least one amino acid given for the respective position is respectively substituted by following amino acids:

a small neutral amino acid for A in position 8;
an acidic or neutral amino acid for E in position 9;

a neutral amino acid for G in position 10; and
an acidic amino acid for D in position 15.

10. The composition according to at least one of claims 1 to 9, wherein, in the active substance GLP-1, the amino acid histidine in position 7 is substituted by a neutral amino acid or the D-form or N-acetylated or N-alkylated form of histidine wherein the amino acids for the stated substitutions are in either the D- or L-form, and the amino acid substituted in position 7 is in either its N-acetylated or its N-alkylated form.

11. The composition according to claims 1 to 10, wherein the amino acid lysine in positions 26 and/or 34 is substituted by K†, G, S, A, L, I, Q, M, R and R†, and the amino acid arginine in position 36 is substituted by K, K†, G, S, A, L, I, Q, M and R†.

12. The composition according to claims 1 to 11, wherein the amino acid tryptophan in position 31 is substituted by F, V, L, I, A and Y.

13. The composition according to claims 1 to 12, wherein the modification stated in claim 6 is combined with at least one of the substitutions S for G in position 22, R for Q and A in positions 23 and 24, and Q for K in position 26, or these substitutions are additionally combined with a substitution of D for E in position 21.

14. The composition according to claims 1 to 13, wherein alanine in position 8 is substituted by a small neutral amino acid from the group consisting of S, S†, G, C, C†, Sar, A†, beta-ala and Aib and wherein the acidic or neutral amino acid substituted for glutamic acid in position 9 is selected from the group consisting of E†, D, D†, Cay, T, T†, N, N†, Q, Q†, Cit, MSO and acetyl-K, and wherein the neutral amino acid substituted for glycine in position 10 is selected from the group

consisting of S, S†, Y, Y†, T, T†, N, N†, Q, Q†, Cit, MSO, acetyl-K, F and F†.

15. The composition according to claims 1 to 14, wherein the amino acid substituted for histidine in position 7 is selected from the group consisting of H†, Y, Y†, F, F†, R, R†, Orn, Orn†, M, M†, N-formyl-H, N-formyl-H†, N-acetyl-H, N-acetyl-H†, N-isopropyl-H, N-isopropyl-H†, N-acetyl-K, N-acetyl-K†, P and P†.

16. The composition according to claims 1 to 15, wherein the modified peptide is:

(H†)7-GLP-1(7-37);
(Y)7-GLP-1(7-37);
(N-acetyl-H)7-GLP-1(7-37);
(N-isopropyl-H)7-GLP-1(7-37);
(A†)8-GLP-1(7-37);
(E†)9-GLP-1(7-37);
(D)9-GLP-1(7-37);
(D†)9-GLP-1(7-37);
(F†)10-GLP-1(7-37);
(S)22(R)23(R)24(Q)26-GLP-1(7-37); and/or
(S)8(Q)9(Y)16(K)18(D)21-GLP-1(7-37).

17. The composition according to claims 1 to 16, wherein a peptide is used which has an increased resistance to degradation in the plasma as compared to GLP-1(7-34), GLP-1(7-35), GLP-1(7-36) or GLP-1(7-37) or the C-terminal amide, and/or has at least one of the following modifications:
(α) substitution of histidine in position 7 by the D-form of a neutral or acidic amino acid or the D-form of histidine;

(β) substitution of alanine in position 8 by the D-form of an amino acid; and

(χ) substitution of histidine in position 7 by an N-acylated (1-6C) or N-alkylated (1-6C) form of an alternative amino acid or histidine.

18. The composition according to claim 17, wherein histidine in position 7 is substituted by an amino acid from the group consisting of P†, D†, E†, N†, Q†, L†, V†, I† and H†.

19. The composition according to claim 17 or 18, wherein the D-amino acid in position 8 is substituted by an amino acid from the group consisting of P†, V†, L†, I† and A†.

20. The composition according to any of claims 17 to 19, wherein the D-amino acid in position 8 is substituted by an alkylated or acetylated amino acid from the group consisting of P, D, E, N, Q, V, L, I, K, and H.

21. The composition according to any of claims 17 to 20, wherein the modified peptide is:

(H†)7-GLP-1(7-37);
(N-acetyl-H)7-GLP-1(7-37);
(N-isopropyl-H)7-GLP-1(7-37);
(N-acetyl-K)7-GLP-1(7-37); and/or
(A†)8-GLP-1(7-37).

22. The composition according to any of claims 1 to 21, wherein the active substances are present in a phosphorylated, acetylated and/or glycosylated form.

23. The composition according to any of claims 2 to 22, wherein the active substance B is a non-specific phosphodiesterase inhibitor, such as:

papaverine;
theophylline;
enprofyllines; and/or
IBMX.

24. The composition according to any of claims 2 to 23, wherein the active substance B is a specific phosphodiesterase inhibitor.

25. The composition according to any of claims 2 to 24, wherein the phosphodiesterase inhibitors which inhibit group III phosphodiesterases (cGMP-inhibited phosphodiesterases) are:

indolidane (LY195115);
cilostamide (OPC 3689);
lixazinone (RS 82856);
Y-590;
imazodane (CI914);
SKF 94120;
quazinone;
ICI 153,110;
cilostazole;
bemorandane (RWJ 22867);
siguazodane (SK&F 94-836);
adibendane (BM 14,478);
milrinone (WIN 47203);
enoximone (MDL 17043);
pimobendane (UD-CG 115);
MCI-154;
saterinone (BDF 8634);
sulmazole (ARL 115);
UD-CG 212;
motapizone;
piroximone;
ICI 118233

26. The composition according to any of claims 2 to 25, wherein the phosphodiesterase inhibitors which inhibit group IV phosphodiesterases (cAMP-specific phosphodiesterases) are:

rolipram ZK 62711; pyrrolidone);
imidazolidinone (RO 20-1724);
etazolate (SQ 65442);
denbufylline (BRL 30892);
ICI63197;
and/or RP73401.

27. The composition according to any of claims 2 to 26, wherein the phosphodiesterase inhibitors which inhibit both group III and group IV phosphodiesterases are:

tolafentrine;
zardaverine;
EMD54622; and/or
Org30029.

28. A compound having the general formula:

R-NH-HAEGTFTSDVSSYLEGQAAKEFIAWLVK-$CONH_2$,

wherein R = H or an organic compound having from 1 to 10 carbon atoms.

29. The compound according to claim 28, wherein R is the residue of a carboxylic acid.

30. The compound according to claim 29, wherein R is formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.

31. A medicament containing an effective amount of the composition according to any of claims 1 to 27 or a compound according to any of claims 28 to 30 for the therapy of insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, MODY (maturity-onset diabetes in young people), for the treatment of secondary hyperglycemias in connection with pancreatic diseases (chronic pancreatitis, pancreasectomy, hemochromatosis) or endocrine diseases (acromegaly, Cushing's syndrome, pheochromocytoma or hyperthyreosis), for the treatment of drug-induced hyperglycemias (benzothiadiazine saluretics, diazoxide or glucocorticoids), for the therapy of pathologic glucose tolerance, for the therapy of hyperglycemias, for the therapy of dyslipoproteinemias, for the therapy of adiposity, for the therapy of hyperlipoproteinemias and/or hypotensions.

32. The medicament according to claim 31, characterized in that said medicament is in a release form by which release is achieved permanently or in a pulsatile way.

33. The medicament according to claim 32, characterized in that said medicament is suitable for subcutaneous, intravenous, peroral, intramuscular or transpulmonary administration.

34. Use of a composition containing at least two of the following active substances A, B, C, wherein:

A = at least one hormone stimulating the production of cAMP;

B = at least one substance inhibiting the degradation of a cyclic nucleotide;

C = at least one hormone stimulating the production of cGMP;

for the preparation of a medicament for the treatment of adiposity.

Abstract

A composition containing at least two of the following active substances A, B, C, wherein:

A = at least one hormone stimulating the production of cAMP;

B = at least one substance inhibiting the degradation of a cyclic nucleotide;

C = at least one hormone stimulating the production of cGMP.

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN FOR APPLICATION BASED ON PCT; PARIS CONVENTION; NON PRIORITY OR PROVISIONAL APPLICATIONS

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P65123US0

101 102

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

COMPOSITION FOR THE THERAPY OF DIABETES MELLITUS AND ADIPOSITY

which is described and claimed in:

- [ ] the attached specification
- [X] PCT International Application No. **PCT/EP98/05804** filed **11 September 1998**
- [X] the specification in application Serial No. **09/508,083** filed **13 March 2000**

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103 104

Prior Foreign Application(s)			Priority Claimed	
197 40 081.7 (Number)	**Germany** (Country)	**12 September 1997** (Day/Month/Year Filed)	[X] Yes	[ ] No
197 57 739.3 (Number)	**Germany** (Country)	**23 December 1997** (Day/Month/Year Filed)	[X] Yes	[ ] No
198 10 515.0 (Number)	**Germany** (Country)	**11 March 1998** (Day/Month/Year Filed)	[X] Yes	[ ] No

I hereby claim the benefit under Title 35, United States Code,§119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

105

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 06/06/2000	DATE 06/06/2000	DATE June 6, 2000

[ ] Additional inventors are named on separately numbered sheets attached hereto.

JACOBSON, PRICE, HOLMAN & STERN, PLLC
ADDITIONAL INVENTORS

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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 204 *	**SIGNATURE OF INVENTOR 205 ***	**SIGNATURE OF INVENTOR 206 ***
DATE 06/06/2000	**DATE**	**DATE**
SIGNATURE OF INVENTOR 207 *	**SIGNATURE OF INVENTOR 208 ***	**SIGNATURE OF INVENTOR 209 ***
DATE	**DATE**	**DATE**
SIGNATURE OF INVENTOR 210 *	**SIGNATURE OF INVENTOR 211 ***	
DATE	**DATE**	

□ Additional inventors are named on separately numbered sheets attached hereto.

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Application deficiencies were found during scanning:

☒ Page(s) 9-25 of Specifications were not present for scanning. (Document title)

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